REMARKS

Entry of the present amendment and reconsideration of the above-referenced application is respectfully requested. Claims 1-29 and 31-37 are pending. Claims 1-14 and 27 have been withdrawn from consideration. Claim 31 has been amended to depend from pending claim 29.

CLAIM 36

Claim 36 stands rejected under 35 U.S.C. §112, 2nd paragraph as being indefinite for not limiting the scope of independent claim 29. Applicants respectfully traverse this rejection. Claim 29 relates to a vegetative cell immobilized within a solid network defining macropores, whereas claim 36 relates to a vegetative cell entrapped within the solid network. Applicants respectfully submit that immobilization by entrapment is not inherent in claim 29, as suggested by the rejection, since macropore diameters can be significantly larger than the size of a vegetative cell within the solid network. Therefore, vegetative cells can be immobilized within the solid network without being entrapped.

CLAIMS 26 AND 29

Independent claims 26 and 29 stand rejected under 35 U.S.C. §103(a) as obvious over Uo et al. (J. Ceram. Soc. Jpn. 100, p. 426-429) and Hino et al. (US 4,148,689).

Applicants respectfully traverse the rejection.

Claim 26 relates to a method that includes mixing a vegetative cell into a sol, mixing a sufficient amount of a dispersant into said sol to cause macropores in a gel formed by the sol; and gelling the sol to form the gel. Claim 29 relates to a gel that includes a solid network formed by the condensation of hydroxy metallates from a sol solution and a vegetative cell added to the sol solution and thereby immobilized within said solid network. The solid network defines macropores.

In rejecting claims 26 and 29, the Examiner has asserted that it would have been obvious to replace the yeast spores of Uo et al. with vegetative cells described by Hino et al. Applicants respectfully disagree with this assertion and traverse the rejection.

There is no reason to believe that one of ordinary skill in the art would find any suggestion to combine the references and to add or mix vegetative cells from Hino et al. into a sol from Uo et al. Firstly, Uo et al. expressly teach away from adding or mixing vegetative cells

into their sols since they purposely selected yeast spores, and not vegetative yeast cells, for immobilization. See, e.g., Uo et al., Section 2.2, page 427. To neglect this express teaching of Uo et al. is to combine references that teach away from their own combination and to engage in hindsight-based reconstruction of the claimed invention.

Secondly, alcohols, such as the methanol present in the sol solutions of Uo et al. are recognized as effective antimicrobial agents. See, e.g., Chapter 12 of the 5th Edition of *Disinfection, Sterilization, and Preservation* edited by Seymour Block[1] (submitted herewith), which discusses the antimicrobial properties of alcohols in general, and methanol in particular, toward, e.g., both vegetative bacteria[2] and bacterial spores.[3] Assuming that the spore suspensions of Uo et al. are entirely water and that the tetramethylorthosilicate (TMOS) in the starting solution completely prehydrolyzes,[4] Uo et al.'s gelation solutions are approximately 45-55 vol.% methanol.[5] The yeast spores in Uo et al. are exposed to these solutions for over one day. Attention is respectfully directed to table 12.4 on page 235 of Block which describes that 65 vol.% methanol is microbicidal to both *Staphylococcus aureus* and *Escherichia coli* in under one minute in suspension tests, and that 9 vol.% methanol is effective at inhibiting *S. aureus* growth. Attention is further directed to table 12.7 on page 236 of Block which illustrates that germicidal activity can be achieved with decreased concentrations of ethanol when exposure time is increased.

Finally, the Office action cites col. 20, lines 44-45 of Hino et al. as supporting the proposition that Hino et al. suggest that vegetative cells can be added or mixed into sols having concentrated organic solvents. Applicants respectfully disagree with this reading of Hino et al. and in fact submit that the results described in Hino et al. are consistent with microbicidal

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[1] Lippincott Williams & Wilkins, Philadelphia, PA, U.S.A. (2001).
[2] Page 234-238 of Block.
[3] Page 238-239 of Block.
[4] Uo et al. prehydrolyze starting solutions for 1 day at 20°C in sealed containers. See, e.g., section 2.3 of Uo et al.
[5] Attention is respectfully directed to Table 3 of Uo et al. which lists the compositions of starting solutions for the immobilization of yeast spores. If one assumes that the spore suspension is entirely water, then Composition A includes approximately 17 moles of water, and Composition B includes approximately 11 moles of water. After complete hydrolysis of the TMOS in the starting solution, Compositions A and B each include approximately 6 moles of methanol (2 moles added and 4 moles released by hydrolysis of 1 mole of TMOS). The methanol/water molar ratios of Compositions A and B before spore addition are approximately 6:17 and 6:11, respectively. Methanol has a gram molecular weight of 32.04 g/mol and a density of 0.791 g/mL. Water has a gram molecular weight of 18.02 g/mol and a density of 1.0 g/mL. Neglecting volume contraction, Compositions A and B each include approximately 243 mL of methanol, Composition A includes approximately 298 mL of water, and Composition B includes approximately 193 mL of water.

activity of alcohols. In particular, Hino et al. describe that sols containing cells can be extrusion cast into organic solvents. See, e.g., col. 20, lines 44-45 and col. 9, line 14-22 of Hino et al. In the example of extrusion casting detailed by Hino et al., the gels were freeze-dried immediately after extrusion and the relative activity of *Erwinia herbicola* after casting in isopropyl alcohol was approximately 61% of the control activity, whereas activities of 84-90% of control were obtained without casting. See, e.g., Tables 6 and 7, and col. 14, line 54-col. 16, line 22 of Hino et al. It appears that the immediate freeze drying represents an attempt to minimize exposure of *E. herbicola* to isopropyl alcohol (due to microbicidal activity of isopropyl alcohol described, e.g., in tables 12.4 and 12.5 on page 235 of Block), and that even this attempt was only partially successful since a decrease in activity relative to uncast gels was nevertheless observed. In conclusion, Hino et al. simply do not describe or suggest mixing vegetative cells into sols with organic solvents and instead provide further empirical evidence consistent with the microbicidal activity of alcohols.

Applicants respectfully submit that both cited references, as well as a common understanding of the microbicidal properties of alcohols, teach away from the proposed combination. Thus, there is no suggestion to combine the cited references, and a *prima facie* case of obviousness has not been established. Applicants therefore respectfully submit that claims 26 and 29, along with the claims dependent therefrom, are patentable over the cited art.

CLAIM 28

Independent claim 28 stands rejected under 35 U.S.C. §103(a) as obvious over Uo et al. and Hino et al.

Applicants respectfully traverse the rejection.

Claim 28 relates to a gel that includes a macroporous solid network and a bacterial cell. In rejecting claim 28, the Examiner has asserted that it would have been obvious to replace the spores in the macroporous solid network of Uo et al. with the bacterial cells described by Hino et al. Applicants respectfully disagree with this assertion and traverse the rejection.

As discussed above, both references teach away from exposure of organisms other than yeast spores to the kinds and concentrations of organic solvents found in the sols of Uo et al.. Although Block describes that the sporicidal activity of alcohols against bacterial spores may be

limited, alcohols are still sporicidal. See, e.g., page 238-239 of Block. Further, neither Uo et al. nor Hino et al. describe the immobilization of bacterial spores.

Applicants therefore respectfully submit that a *prima facie* case of obviousness of claim 28 has not been established. Applicants therefore respectfully submit that claim 28 is patentable over the cited art.

CLAIM 15

Independent claim 15 stands rejected under 35 U.S.C. §103(a) as obvious over Uo et al., Hino et al., Klein et al. (Better Ceramics Through Chemistry: MRS Symp. Proc. Vol. 32, p. 33-39), and Rao et al. (J. Sol-Gel Sci. Tech. 3, p. 205-217).

Applicants respectfully traverse the rejection.

Claim 15 relates to a sol that includes P moles of a hydroxy metallate, W moles of water, a sufficient amount of a dispersant to cause macropores in a gel formed by said sol, and a biological material. The ratio of W:P is greater than 25:1.

None of Uo et al., Hino et al., or Rao et al. describe sol solutions with a water to hydroxy metallate ratio greater than 25:1.

Klein et al. describe a sol solution with a water to hydroxy metallate ratio of 32:1. In Klein et al., the sol solutions with elevated water to hydroxy metallate ratios have additional ethanol to permit solubility of the increased water in the sol solution. See, e.g., Klein et al., page 34, last sentence of the second paragraph. In particular, the sol solution with a W:P ratio of 32:1 has four times as much ethanol as the sol solutions with W:P ratios of 4:1. See, e.g., page 34, second paragraph of Klein et al. Assuming that the tetraethylorthosilicate (TEOS) in the sol solution completely prehydrolyzes, Klein et al.'s sol solutions are approximately 65 vol.% ethanol.[6] The sol solutions of Klein were capped, heated to 80°C, and allowed to react for two days. Attention is respectfully directed to pages 231-232 of Block where alcohol-induced protein coagulation and plasma membrane lysis is described, table 12.6 on page 235 of Block

[6] Attention is respectfully directed to paragraph 2, page 34 of Klein et al. which describes the compositions of sol solutions of varying hydrolysis ratios. The sol solution with a 32:1 molar ratio of water to TEOS includes a volume of ethanol that is four times the volume of TEOS. TEOS has a gram molecular weight of 208.3 g/mol and a density of 0.934 g/mL, as described in the specification for Sigma-Aldrich product number 13,190-3, tetraethyl orthosilicate, submitted herewith. Thus, for 32 moles of water, the sol solution includes approximately 19.3 moles of ethanol (four moles of ethanol from complete hydrolysis of TEOS and 15.3 moles of ethanol from the 892 ml of ethanol added to solubilize 1 mole (223 ml) of TEOS with 32 moles of water). This ethanol/water molar ratio of 19.3:32 corresponds to an approximately 64 wt.% ethanol solution, which is greater then 65 vol.% ethanol, according to table 12.3 of Block.

which describes that 60-70 vol.% ethanol is effective at killing a number of bacterial species in under one minute, pages 238-239 of Block where the sporicidal activity of ethanol is described, and table 12.10 on page 239 of Block where the viricidal activity of ethanol against a number of viral species is described in terms of minutes and hours. Attention is further directed to table 12.7 on page 236 of Block which illustrates that germicidal activity can be achieved with decreased concentrations of ethanol when exposure time is increased. It is further pointed out that the majority of these investigations were conducted either at room temperature or at physiological temperatures rather than 80°C.

Applicants respectfully submit that, in light of the elevated ethanol concentrations required to obtain solubility of the increased water in Klein et al.'s sols, that one of ordinary skill in the art would find no suggestion to use Klein et al.'s approach to achieving water to hydroxy metallate ratios of greater than 25:1 in a sol that includes a biological material. Indeed, in light of the studies into ethanol activity and express statements in Uo et al. discussed above, not only is a suggestion to combine the cited art missing but one of ordinary skill in the art would actually be discouraged from combining the cited references as suggested.

Since there is no suggestion to combine the cited references in the manner suggested, and in fact combination of the references is discouraged, a *prima facie* case of obviousness has not been established.

Applicants therefore respectfully submit that claim 15, and the claims dependent therefrom, are patentable over the cited art.

In view of the above remarks, all of the claims should be in condition for allowance. A formal notice to that effect is respectfully solicited.

The present amendment is submitted in accordance with the provisions of 37 C.F.R. §1.116, which after final rejection permits entry of amendments placing the claims in better form for consideration on appeal. As the present amendment amends improperly dependent claim 31

and is believed to overcome the outstanding rejections under 35 U.S.C. §103(a), the present amendment places the application in better form for consideration on appeal. It is therefore respectfully requested that 37 C.F.R. §1.116 be liberally construed and the present amendment be entered.

Respectfully submitted,

Date: 7/25/03

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